REMARKS

Applicants thank the Examiner for granting them an interview, which was conducted by telephone on July 19, 2001. Based on that interview, and the subsequent conversation between the Examiner and the undersigned, Applicants understand that the Examiner will enter the present Amendment (the Advisory Action, which indicates that the amendment filed June 11, 2001, would not be entered, notwithstanding). The present amendment cancels all of the claims previously presented except those the Examiner indicated would be allowable (barring any unforeseen discoveries in the Examiner's final search of the prior art). The Examiner indicated the presently pending claims were allowable in view of amendments and arguments of record (or made of record here).

As agreed with Examiner Zeman, it is unnecessary for Applicants to resubmit the three Exhibits that were filed with their Amendment of June 11, 2001. These Exhibits should be a part of the record of the case; Applicants understand that duplicate copies need not be provided here.

Claims 54, 57-59, and 61-87 are pending in the application, claims 55, 56, and 60 having been canceled and claims 68-87 having been added by the present amendment.

The amendment of claim 54 is supported by the specification at, for example, page 5, lines 5-6 and at page 11, lines 2-9. Claims 57-59 and 62-67 have been amended for clarity (to, *e.g.*, correct inadvertent grammatical errors and provide appropriate antecedent basis for the claim terms). Claim 61 has been amended to read as an independent claim. New claims 68, 76, and 84 are supported by the specification at, for example, page 11, lines 9-16. New claims 69, 77, and 85 are supported by the specification at, for example, page 4, lines 29-30. New claim 78 is supported by original claim 41 and by the specification at, for example, page 14, lines 15-17. New claims 70, 71, 82, 83, and 87 are supported by, for example, original claims 3 and 17. New claims 72 and 80 are supported by the specification at, for example, page 24, lines 3-8. New claims 75 is supported by original claim 47 and by the specification at, for example, page 15, lines 18-22. New claims 79 and 81 are supported by the specification at, for example, page 5, lines 7-13 and page 19, lines 8-10. New claim 86 is supported throughout the specification at, for example, page 9, lines 20-27, page 30, lines 16-18, page 31, lines 4-9 and the Examples at pages 34-52. No new matter has been added.

Claim Objections

Claim 66 was objected to as being in an improper form. A multiply dependent claim should refer to other claims in the alternative only, but claim 66 depended from claim 64 and claims 55-62 (Office Action at page 2).

Claim 66 has been amended to refer to other claims in the alternative only. Therefore, this objection may now be withdrawn.

Claims 57 and 60 were objected to because they recited a variety of abbreviations that were not spelled out at their first appearance in the claims (Office Action at page 2).

Claim 60 has been cancelled, and there is no apparent alternative to the terms used in claim 57. Claim 57 includes the terms M1, M2, P1, P2, and PA, which are used routinely by those of ordinary skill in the art. Upon investigation, Applicants' representative could find no alternative names for these antigens, *i.e.*, the terms used do not appear to be abbreviations. The Examiner's attention is directed to the pages from *Virology*, Lippincott-Raven, Philadelphia, Fields *et al.*, eds., 3rd Edition, 1996 (pages 90, 1358, and 1366; attached as Exhibit A to the Amendment filed June 11, 2001), where the terms M1, M2, PB1, PB2, and PA are introduced, as if complete. Accordingly, this ground for rejection should be withdrawn.

Claim 58 was objected to for reciting "pET65MP/NP-B" and "pET65M/NP/D" as if they were, themselves, proteins. The Examiner is correct in supposing that these terms represent plasmids that encode fusion proteins. Claim 58 has been amended to make this clear. Thus, the objection may now be withdrawn.

Applicants' Declaration

The declaration filed on May 24, 2000, under 37 C.F.R.§ 1.131 was found ineffective to overcome Suzue *et al.* (*J. Immunol.* 156:873-879, 1996; herein, "Suzue"). The Examiner states, however, that a declaration stating "that the work was done in the USA, a WTO country or a NAFTA country" and including "the same evidence and arguments present in the instant declaration would be sufficient to overcome the reference" (Office Action at page 3).

The declaration filed on June 11, 2001, is identical to the declaration filed on May 24, 2000, except that Applicants also declare that "[t]he work described in the Exhibit was conducted in the United States of America or Canada" (see ¶ 6; Exhibit B of the Amendment

filed June 11, 2001). The declaration should, therefore, effectively remove not only Suzue, but also Roman *et al.* (*Immunol.* 88:487-492, 1996; herein, "Roman"). Roman was published after Suzue (*i.e.*, after January 1, 1996).

As neither Suzue nor Roman can be applied against claims in the present application, the rejections based on these references (the rejection of claims 54, 55, 59, and 61-67 for alleged lack of novelty in view of Suzue and the rejection of claims 56-58 for alleged obviousness over Roman and Suzue) must be withdrawn.

New Grounds for Rejection

The Examiner states (Office Action at page 6):

> [a]pplicant has replaced the previously pending claims with claims limited to fusion proteins, but not limited in the nature of the stress protein. These amendments required a new search and the application of new art.

The present action cannot properly be made final. The new ground of rejection is neither necessitated by Applicants' amendment nor based on information submitted in an information disclosure statement. MPEP at 706.07(a). Applicants' amendment limited the compositions claimed to fusion proteins, but these compositions have been before the Examiner since prosecution began. Applicants elected to prosecute the claims of Group I, which included the following claim (claim 5):

> 5. The vaccine of Claim 1 wherein the antigen and the stress protein are linked as a fusion protein.

Thus, the Examiner could have, and should have, searched for art concerning fusion proteins earlier. Nothing in Applicants' amendment necessitated a new search. Accordingly, the Examiner is asked to reconsider and withdraw the "finality" of the present Office Action (and enter the amended claims shown above).

35 U.S.C. § 102(b)

Claims 54, 55, 58, and 61-67 are rejected as being anticipated by Young (WO 94/29459; herein, "Young"). In characterizing Young, the Examiner states (Office Action at page 6; emphasis added):

> * Young discloses fusion proteins of microbial stress proteins and an antigen of interest
>
> * Young sets forth that fusion proteins can be made between a stress protein and any antigen
>
> * Antigens of viral pathogens, bacteria, or cancer cells are specifically contemplated
>
> * The fusion proteins are administered to mice in a pharmacologically acceptable carrier or diluent, phosphate buffered saline

This ground for rejection should be withdrawn in view of the present amendment. As the Examiner knows, "[t]o anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter." *PPG Industries, Inc. v. Guardian Industries Corp.* 75 F.3d 1558 (Fed. Cir. 1996). Young does not "disclose every element" of the present claims. Each of the present independent claims is limited to a fusion protein (or compositions containing it, or methods of using it) that includes a stress protein, or a portion thereof, and a particular antigen or an antigenic portion thereof. For example, claim 54 is limited to a fusion protein comprising an antigen of the influenza virus and claim 75 is limited to a fusion protein comprising a human papillomavirus (HPV) antigen. Young does not disclose an antigen of the influenza virus or an HPV antigen. Therefore, Young cannot anticipate the present claims.

Young's disclosure of generic fusion proteins is not enough. While the earlier disclosure of a species defeats a claim to the genus encompassing it, the opposite is not true. *In re Gosteli*, 872 F.2d 1008 (Fed. Cir. 1989). An earlier disclosure of the genus does not anticipate each and every species within it. For example, in *Corning Glass Works v. Sumitomo Electric U.S.A.*, the patent at issue claimed germania as a dopant for use in an optical waveguide fiber. Although the prior art disclosed waveguide fibers with doped cores, and suggested titania as the dopant, the court found the claims covering the use of germania were not anticipated. The court noted that

the prior art did not expressly disclose germania, nor did it exclude it. 868 F.2d 1251 (Fed. Cir. 1989).

The facts of the present case are entirely consistent with those in *Corning Glass*. Here, Applicants claim fusion proteins containing specific antigens that were neither disclosed in, nor excluded by, the prior art. The rejection for anticipation should therefore be withdrawn.

35 U.S.C. § 103

Claims 56-58 and 60 are rejected as being obvious over Young in view of Srivastava (U.S. Patent No. 5,837,251; herein, "the '251 patent"). Claim 60 has been cancelled. Claim 56 has also been canceled, but the limitation of that claim (that the antigen is an antigen of the influenza virus) has been incorporated into amended claim 54.

As a preliminary matter, Applicants note that claims 61-67 are not rejected as being obvious. For the reasons described above, these claims cannot, as a matter of law, be rightfully rejected for lack of novelty. Accordingly, at least claims 61-67 are now in condition for allowance (claim 61 has been rewritten as an independent claim), which action is respectfully requested.

In describing the basis for the obviousness rejection of claims 56-58 and 60, the Examiner reiterates her characterization of Young (Office Action at pages 7-8), and then states that the '251 patent "discloses complexes of hsp proteins from the hsp60, hsp70 and hsp90 families in complex with antigens such as tumor antigens or influenza antigens" (Office Action at page 8).[1] After stating that the '251 patent "discloses the benefits of combining viral antigens and cancer antigens with a stress protein, and Young discloses that those antigens in fusion with one another provide good T cell reactivity upon immunization," the Examiner argues that one "would have been motivated to create a fusion protein comprising the influenza or cancer antigen in fusion with the stress protein so that the two moieties would be sure to stay together throughout the antigen presentation process, ensuring a better response" (Office Action at page 8).

[1] The complexes disclosed in the '251 patent are strictly limited to non-covalent complexes; fusion proteins are not suggested in any way.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference(s) must teach or suggest all the claim limitations. MPEP at 2143. Neither the first nor the second requirements are met with respect to claim 54, which now carries the limitation previously recited in claim 56, or amended claims 57 and 58.

Nothing in Young or the '251 patent provides the motivation to modify or combine their teachings, and the Examiner appears to clearly recognize that. Instead of using the references to establish the requisite motivation, the Examiner argues, as noted above, that one of ordinary skill in the art would have been motivated to make the claimed fusion proteins because the two moieties within a fusion protein "would be sure to stay together throughout the antigen presentation process" and this would ensure "a better response" (Office Action at page 8). Thus, the Examiner's case of *prima facie* obviousness relies on the "skill in the art" component. This component is rarely sufficient to support an obviousness rejection, and it cannot do so here. In *Al-Site Corp. v. VSI Intern., Inc.*, VSI attempted to invalidate Al-Site's patent by arguing, *inter alia*, that the claimed subject matter (a hanger for displaying non-prescription eyeglasses) was obvious. 174 F.3d 1308 (Fed. Cir. 1999). VSI was unable to point to any specific teaching or suggestion for making the claimed combination of elements, so it relied instead on what it presumed to be the level of ordinary skill in the art at the time of the invention to supply the missing suggestion to combine. VSI's argument failed, the court stating (*Al-Site* at 1324):

> In the first place, the level of skill in the art is a prism or lens through which a judge or jury views the prior art and the claimed invention. This reference point prevents these deciders from using their own insight or, worse yet, hindsight, to gauge obviousness. Rarely, however, will the skill in the art component operate to supply missing knowledge or prior art to reach an obviousness judgment. *See W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983) ("To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher."). Skill in the art does not act as a bridge over gaps in substantive presentation of an obviousness case, but instead supplies the primary guarantee of objectivity in the process.

The Examiner is attempting to bridge an important gap in this case with nothing more than an unsupported statement concerning what one of ordinary skill in the art might think. But, as in *Al-Site*, the gap cannot be bridged (VSI supported their contention with prior art patents and still failed). The facts cannot support the conclusion that one of ordinary skill in the art would have been motivated to use the influenza antigens disclosed in the '251 patent as part of a fusion protein. There is simply nothing upon which to base the presumption that the components of a fusion protein would "stay together" any better than the components of the protein complexes in the '251 patent. Indeed, the '251 patent teaches that non-covalent hsp-containing complexes occur naturally in patients. For example, the '251 patent teaches (8:57-67; emphasis added):

> The methods of the invention comprise methods of eliciting an immune response in an individual in whom the treatment or prevention of infectious diseases or cancer is desired by administering a composition comprising an effective amount of a complex, in which the complex consists essentially of a hsp noncovalently bound to an antigenic molecule. In a preferred embodiment, the complex is autologous to the individual; that is, the complex is isolated from either [from] the infected cells or the cancer cells for precancerous cells of the individual himself (e.g., preferably prepared from infected tissues or tumor biopsies of the patient).

The complexes can also be isolated from healthy individuals. The '251 patent teaches that (6:12-14; emphasis added):

> Alternatively, the hsp and or the antigenic molecule can be isolated from ... others [*i.e.*, one other than the patient]

Thus, the non-covalent protein complexes described in the '251 patent are stable under normal physiological conditions (otherwise they could not be isolated from healthy individuals), as well as under extreme physiological conditions (*i.e.*, when the cell is infected, cancerous, or exposed to another form of stress, such as heat; that is, after all, how hsps exert their protective effect – by complexing with other proteins). There is no evidence that fusion proteins would be more stable (a covalent bond is not invincible), nor is there any evidence that those of ordinary skill in the art would presume as much. This is the Examiner's supposition, made with full knowledge of Applicants' success

with fusion proteins, but it cannot be fairly attributed to one of ordinary skill in the art at the time the invention was made.

Furthermore, even if there was reason to presume that fusion proteins will "stay together," nothing suggests that they will produce a "better response" than the non-covalent complexes of the '251 patent. To the contrary, it was known in the art that recombinant proteins (which fusion proteins would necessarily be) are not as immunogenic as polymeric proteins (such as non-covalently bound protein complexes). For example, in the background section of his U.S. Patent (No. 4,918,166, a copy of which was attached as Exhibit C to the Amendment filed June 11, 2001), Kingsman states (emphasis added):

> A substantial disadvantage of most antigens produced by recombinant DNA techniques for vaccines is that they are usually made as simple monomeric proteins. This is not the ideal configuration for an immunising antigen as it does not readily permit the cross-linking of the components of the immune system that is required for maximum stimulation of humoral and cellular immunity. An ideal immunogen is a polymer of multiple antigenic determinants assembled into a high molecular weight carrier. A good immunogen should also have the maximum number [of] epitopes exposed. This is best achieved by presenting multiple copies of the antigen on the surface of a particle.

In view of the foregoing, it should be clear that there is no motivation to combine Young and the '251 patent to arrive at the subject matter now claimed. On this basis alone, the rejection for obviousness should be withdrawn.

The prior art of record also fails to supply a reasonable expectation of success. The consistent criterion for determining obviousness has been whether the prior art suggests to one of ordinary skill in the art that the claimed invention should be carried out and would have a reasonable likelihood of success – both the suggestion and the expectation of success must be found in the prior art. *In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988). As one of ordinary skill is charged with knowledge of the entire body of technological literature, one would necessarily be aware of the teaching of Kingsman (see the excerpt above). Given that teaching, Applicants had, at most, only an invitation to experiment, and that is not sufficient to maintain a rejection for obviousness. The prior art cannot provide a reasonable expectation for success with

fusion proteins containing the particular antigens now claimed. This ground for rejection should be withdrawn.

Attached is a marked-up version of the changes being made by the current amendment. Applicants ask that all claims be examined. Please apply any charges, or any credits, to Deposit Account No. 06-1050, referencing Attorney Docket No. 12071-011002.

Respectfully submitted,

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Version with markings to show changes made

In the claims:

Claims 55, 56, and 60 have been cancelled.

Claims 54, 57-59, and 61-67 have been amended as follows.

54. (Amended) A fusion protein comprising an antigen of an influenza virus, or an antigenic portion thereof, and a stress protein, or a portion [of the amino acid sequence of the stress protein] thereof, wherein the [stress] fusion protein [or the portion thereof is able to induce a cell mediated cytolytic] induces an immune response against the antigen in a mammal to whom the fusion protein is administered.

57. (Amended) The fusion protein of claim [56] 54, wherein the antigen of the influenza virus is [selected from the group consisting of] hemagglutinin, nucleoprotein, neuraminidase, M1, M2, PB1, PB2, or PA [and a combination thereof].

58. (Amended) The fusion protein of claim 54, wherein the fusion protein is [selected from the group consisting of] encoded by plasmid pET65MP/NP-B [and] or plasmid pET65MP/NP-D.

59. (Amended) The fusion protein of claim 54, wherein the antigen includes a [cytolytic T cell] CTL epitope.

61. (Amended) [The] A fusion protein [of claim 54 wherein the stress protein is] comprising an antigen of the influenza virus, or an antigenic portion thereof, and a bacterial stress protein, or a portion thereof, wherein the fusion protein induces an immune response against the antigen in a mammal to whom the fusion protein is administered.

62. (Amended) The fusion protein of claim 61, wherein the bacterial stress protein is a mycobacterial stress protein.

63. (Amended) [The] A composition comprising the fusion protein of [any one of claims 54-62, in combination with] of claim 54 and a pharmaceutically acceptable excipient, carrier, diluent, or vehicle.

64. (Amended) A method of inducing [a cell mediated cytolytic] an immune response against an antigen of an influenza virus, the method comprising administering the fusion protein of claim 54 to a vertebrate in an amount effective to induce an immune response [a fusion protein according to claim 54] against the antigen.

65. (Amended) The method of claim 64, wherein the fusion protein is administered in combination with a pharmaceutically acceptable excipient, carrier, diluent, or vehicle.

66. (Amended) [The] A method of inducing an immune response against an antigen of the influenza virus, the method comprising administering the fusion protein of [claim 64 with the fusion protein of any one of claims 55-62] claim 58 to a vertebrate in an amount effective to induce an immune response against the antigen.

67. (Amended) The method of claim 66, wherein the fusion protein is administered in combination with a pharmaceutically acceptable excipient, carrier, diluent, or vehicle.